

High Dose Dipyridamole Echocardiography Test in Effort Angina Pectoris

EUGENIO PICANO, MD, FABIO LATTANZI, MD, MICHELE MASINI, MD,
ALESSANDRO DISTANTE, MD, ANTONIO L'ABBATE, MD, FACC

Pisa, Italy

The dipyridamole echocardiography test (intravenous dipyridamole with two-dimensional echocardiographic monitoring) was performed in 93 patients with effort chest pain and in 10 control subjects. The test was considered positive when regional asynergy appeared after dipyridamole administration. When negative at the low dose (0.56 mg/kg body weight in 4 minutes), the test was repeated on a different day with a higher dose (0.84 mg/kg in 10 minutes). All 93 patients underwent coronary arteriography; 72 of them had significant (>70% luminal reduction) coronary artery disease.

Thirty-eight of the 93 patients had a positive low dose dipyridamole echocardiography test; 15 other patients with a negative low dose test had a positive high dose test. All 53 patients with a positive test had significant coronary artery disease; 12 of them had a negative ex-

ercise stress test. In relation to the presence of coronary artery disease, the dipyridamole echocardiography test had an overall specificity higher than that of the exercise stress test (100 versus 71%) and a similar overall sensitivity (74 versus 69%).

The dipyridamole echocardiography test is feasible in all patients with a good baseline echocardiogram. It detects the site of apparent ischemia more precisely than does an exercise stress test, and can unmask electrocardiographically silent ischemia. If performed in patients with a negative low dose dipyridamole echocardiography test, the high dose test adds sensitivity (probably by achieving maximal dilation in patients in whom the low dose is only partially effective), without any loss in specificity and with no apparent increase in risk.

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The dipyridamole echocardiography test is feasible and useful in patients with effort angina pectoris (1); perhaps its major limitation is a relatively low sensitivity. In our previous study (1), the standard dose of 0.56 mg/kg body weight in 4 minutes—employed for thallium-201 imaging studies (2,3)—was used. Such a dose usually provides maximal coronary vasodilation, but there is a small risk that in some patients the dose is insufficient (4). Conceivably, the sensitivity of the test could be augmented by the use of a higher dose.

We therefore performed a dipyridamole echocardiography test at the standard dose in 93 consecutive patients with effort chest pain who did not overlap with the patient group of our previous study. In the patients with a negative

test, we repeated the test on a different day at a higher dose of 0.84 mg/kg in 10 minutes, which should achieve maximal coronary dilation in virtually all patients (4). In this way, the test could theoretically detect the false negative results due to the incomplete pharmacologic effect of the dose employed. Available clinical experience with similar high doses (ranging from 0.75 to 1 mg/kg in 10 minutes) suggests that no significant increase in risk takes place (5-11).

Methods

Characteristics of patients. One hundred two patients with a presumptive diagnosis of coronary artery disease, characterized by a history of either typical or atypical effort pain, were initially considered. Patients with unstable angina, cardiac failure, congenital or valvular heart disease, conduction disturbances or documented cardiomyopathy were not included in this group. Nine patients were excluded from the set of 102 because of poor quality two-dimensional echocardiographic baseline images. Thus, 93 patients (78 men, 15 women) with a mean age of 55 years (range 37 to 76) were enrolled in the study.

From the Istituto di Fisiologia Clinica del CNR, Pisa, Italy. Dr. Picano is the recipient of the A.R.M.E.D. (Associazione per la ricerca in medicina) Research Fellowship for Ultrasonic Diagnosis of Atherosclerosis, Pisa, Italy. This study was presented in part at the 58th Scientific Meeting of the American Heart Association, Washington, D.C., November 11 to 14, 1985.

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Address for reprints: Eugenio Picano, MD, Istituto di Fisiologia Clinica del CNR, Via Savi 8, 56100 Pisa, Italy.

Seventeen patients had a previous myocardial infarction with diagnostic serum enzyme or electrocardiographic changes, or both. Patients entering the study had discontinued treatment with calcium channel blockers or nitrates, or both, for at least 48 hours, and use of beta-adrenergic blocking agents for at least 15 days. All patients gave informed consent before entering the study. Before coronary angiography, all patients performed, in random order and on different days, an exercise stress test and a dipyridamole echocardiography test.

We also studied a control group of 10 subjects (ages 20 to 25 years). All these subjects were asymptomatic, had a negative exercise stress test and no family history of coronary artery disease.

Exercise electrocardiography. All patients performed a multistage bicycle ergometer test, with an initial load of 25 W and subsequent increments of 25 W every 2 minutes. A 12 lead electrocardiogram and blood pressure determination were performed at baseline and thereafter every minute. Criteria for interrupting the test were severe chest pain, diagnostic ST segment shift, fatigue, limiting dyspnea or maximal predicted heart rate in absence of ischemia.

Electrocardiographic tracings were considered diagnostic for myocardial ischemia when there was an ST segment shift of at least 0.15 mV, 0.08 second after the J point compared with baseline.

Dipyridamole echocardiography test. Dipyridamole was administered intravenously at a dose of 0.56 mg/kg in 4 minutes, during continuous echocardiographic monitoring, as previously described (1). In patients with a negative test, the test was repeated on the next day at a higher dose: 0.56 mg/kg in 4 minutes followed by 4 minutes of no dose and then 0.28 mg/kg in 2 minutes. The cumulative dose was therefore 0.84 mg/kg in 10 minutes.

During the procedure, the blood pressure was recorded each minute with a cuff sphygmomanometer. A 12 lead electrocardiogram was performed before and every minute after starting the intravenous infusion. Some leads (usually V₂ and V₄) were slightly displaced to avoid interfering with the positioning of the transducer. Aminophylline (240 mg), which promptly reverses the effects of dipyridamole, was ready for immediate use. Patients were instructed to fast for at least 3 hours before the test and specifically to avoid coffee and tea.

Electrocardiographic tracings were considered diagnostic for myocardial ischemia when there was an ST segment shift of at least 0.15 mV, 0.08 second after the J point as compared with baseline.

Two-dimensional echocardiograms were continuously recorded during the dipyridamole infusion and up to 20 minutes after the end of the infusion. A commercially available wide angle phased array imaging system (Hewlett-Packard 77020, 3.5 and 5.0 MHz transducers) was used. In the baseline studies, all standard echocardiographic views

were obtained when possible. During the test new areas of abnormal wall motion were identified on multiple views by rapidly moving the ultrasound transducer through various positions. After an optimal position for the observation of abnormal wall motion was established, the transducer was held stationary throughout the remainder of the study and the recovery period.

The videotapes were analyzed by two independent observers. When there was a disagreement about the results (positivity versus negativity), a third observer reviewed the study and the subsequent majority judgment was binding. None of the three observers had access to angiographic and exercise stress test findings before interpretation of the videotapes. Segmental anatomy and wall motion were assessed in a qualitative manner as previously reported (1). Wall motion was graded as hyperkinetic, normal, hypokinetic, akinetic or dyskinetic.

Positivity of the test was linked to detection of a transient asynergy of contraction that was absent or of lesser degree in the baseline examination (for example, hypokinesia at rest becoming akinesia or dyskinesia after dipyridamole administration). Any region that was already dyskinetic in a rest condition was not considered for analysis.

Intraobserver variability was assessed by one of the investigators repeating the evaluation of 30 studies, selected at random, 1 month after the first interpretation and without knowledge of the first evaluation.

Echocardiographic M-mode tracings, generated from a line of view on the two-dimensional image, could be obtained in 20 patients with a positive test. The percent systolic thickening of the region involved by ischemia (as assessed by two-dimensional echocardiography) was measured in baseline conditions and at the peak ischemic phase (just before aminophylline injection).

Angiographic study. All patients underwent selective coronary arteriography, using either the Judkins or the Sones technique. Multiple views of each vessel were filmed. A vessel was considered to have significant obstruction if its diameter was narrowed by 70% or more with respect to the prestenotic tract.

Two independent observers who were unaware of echocardiographic and clinical data analyzed coronary angiograms for the degree of stenosis in the right, left main, left anterior descending (or diagonal) and left circumflex (or marginal) coronary arteries. When there was disagreement about the degree of stenosis, a third observer reviewed the study and the judgment was binding.

Statistical analysis. Differences between the results of the exercise stress test and dipyridamole echocardiography test were compared using the chi-square test; a Fisher's exact test was utilized when appropriate. Hemodynamic and wall motion differences before and after dipyridamole administration were tested for significance by the paired Student *t* test; values are expressed as mean \pm SD.

Results

Dipyridamole echocardiography test. Two-dimensional echocardiographic studies were adequate for analysis and of unchanged quality compared with the baseline examination in all patients. Of the 72 patients with coronary artery disease, 38 (53%) had regional transient asynergy (hypokinesia in 18, akinesia in 20) after the low dose of dipyridamole. Of the remaining 34 patients with coronary artery disease and a negative low dose test, high dose dipyridamole induced asynergy in 15 (hypokinesia in 7, akinesia in 8) (Fig. 1). In these patients, the onset of the asynergy occurred within 0 to 5 minutes after the end of the high dose infusion. In the 53 patients with a positive

Figure 1. Two-dimensional pictures taken from the parasternal long-axis view; end-diastole (E-D) is **above** and end-systole (E-S) is in the **middle**. In the schema **below**, the systolic contour (dashed lines) is superimposed on the diastolic silhouette. In basal conditions (BASAL) a normally contracting septum (S) and posterior wall (PW) are shown. Two minutes after the end of the second infusion of dipyridamole (DIPYR) ischemia develops; the posterior wall is almost akinetic (arrows), whereas the septum exhibits a normal pattern of contraction.

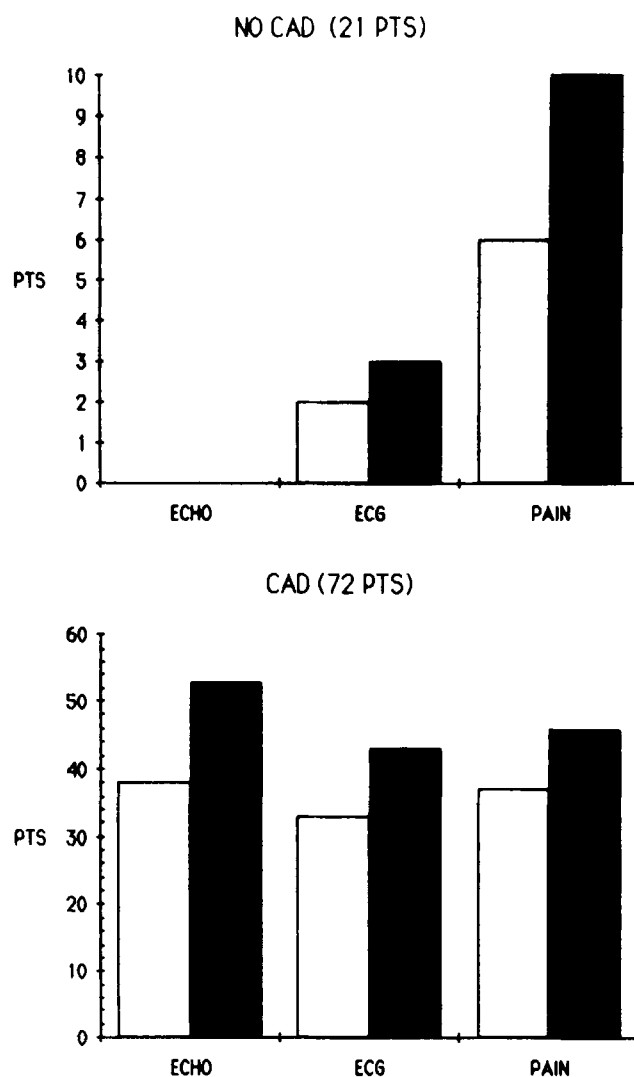
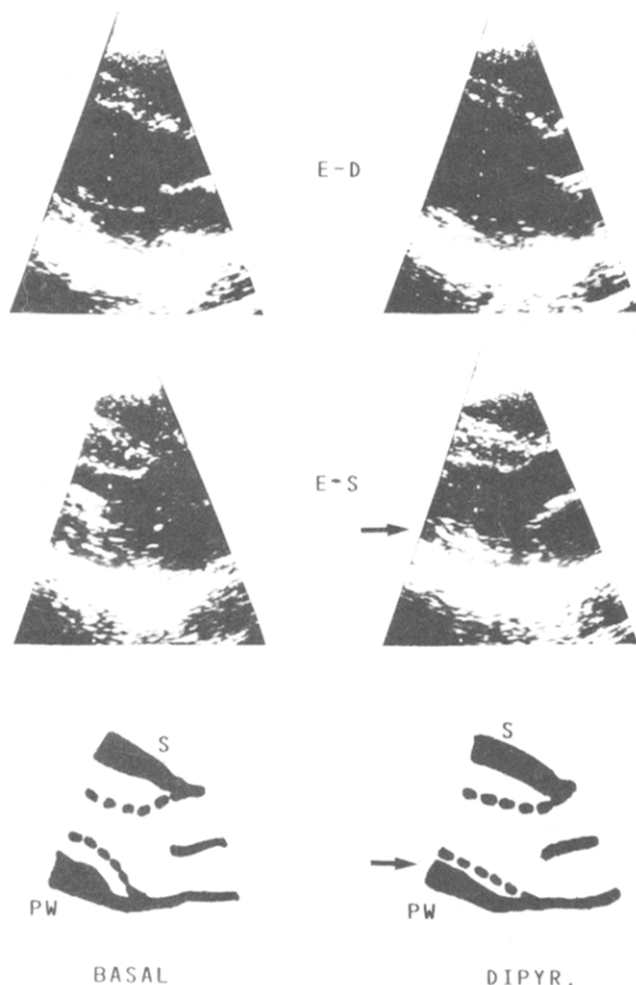


Figure 2. Occurrence of ischemic echocardiographic changes (ECHO), electrocardiographic changes (ECG) and angina (PAIN) in the 21 patients (PTS) without coronary artery disease (NO CAD) and in the 72 patients with significant coronary atherosclerosis (CAD). **Open bars** represent the findings after the low dipyridamole dose (0.56 mg/kg in 4 minutes), **solid bars** after the higher dose (0.84 mg/kg in 10 minutes).

result in the dipyridamole echocardiography test (using both high and low doses), the asynergy mainly involved the septum in 23 patients, inferoposterior wall in 13, anterolateral wall in 10 and apex in 7. No patient without coronary artery disease had a positive test (with either the low or high dipyridamole dose).

In the 20 positive tests in which a M-mode tracing of the ischemic region could be obtained, the percent systolic thickening decreased from $38.7 \pm 9.5\%$ in baseline conditions to $6.7 \pm 7.2\%$ at peak ischemia ($p < 0.01$). The occurrence of chest pain and echocardiographic and electrocardiographic changes after low and high dose dipyridamole

Table 1. Hemodynamic Findings

	CAD Patients With Positive High Dose Tests (n = 15)					CAD Patients With Negative High Dose Tests (n = 19)	
	Low Dose (negative tests)		High Dose (positive tests)			Basal	Maximal
	Basal	Maximal	Basal	Asynergy	Maximal		
Heart rate (beats/min)	72 ± 9	84 ± 12†	77 ± 9	90 ± 12†	95 ± 24†	75 ± 10	95 ± 15†
Systolic blood pressure (mm Hg)	143 ± 12	134 ± 11†	143 ± 13	136 ± 11†	149 ± 14*	144 ± 18	148 ± 21
Diastolic blood pressure (mm Hg)	84 ± 7	77 ± 6†	81 ± 9	75 ± 7†	80 ± 7	83 ± 11	78 ± 12
RPP (× 100) (mm Hg × beats/min)	102 ± 13	112 ± 17†	109 ± 11	121 ± 15†	141 ± 25†	107 ± 20	131 ± 18†

*p < 0.05; †p < 0.01 (significance is compared with basal). Asynergy = onset of asynergy; CAD = coronary artery disease; Maximal = maximal hemodynamic changes; RPP = rate-pressure product.

in the two groups of patients (with and without coronary artery disease) is summarized in Figure 2.

The assessment of positivity versus negativity of the 148 studies analyzed (all 93 low dose tests plus 55 tests repeated at the higher dose) was unanimous in 142. In the remaining six cases there was a split decision. The intraobserver agreement was 100% in the 30 studies reanalyzed by the same observer. This high level of interobserver and intraobserver agreement was made possible by several factors: the quality of echocardiographic tracings was as good after dipyridamole as in baseline conditions; the readers agreed in advance not to record minor degrees of hypokinesia; primary reliance was placed on changes from baseline to peak dipyridamole; and the investigators had previous experience in joint reading (1).

Hemodynamic findings. The findings after high dose dipyridamole in the patients with coronary artery disease are reported in Table 1. In addition, the findings after the negative low dose test are presented for the group with a positive high dose test.

Side effects after dipyridamole. Of the 93 patients given low dose dipyridamole, side effects occurred in 58 (62%); of the 55 patients given high dose dipyridamole, side effects occurred in 38 (69%). No patient had significant arrhyth-

mias, severe hypotension or vomiting after either the low or the high dose test. No side effects were severe and we completed the test in all patients. Headache occurred in 29 (31%) and 20 (36%) with the low and high dose, respectively; mild transient facial flushing in 20 (22%) and 15 (27%), respectively; and mild transient nausea in 12 (13%) and 9 (16%), respectively. Patients who experienced a side effect after the low dose usually also had this effect after the high dose.

Findings in the control group. All the 10 control subjects showed an echocardiographic pattern similar to that of the patients with a negative test: a transient hyperkinetic phase, reaching its peak soon after the end of the infusion, slowly reverting to a normal contraction pattern (usually restored 10 to 15 minutes after the end of the infusion). The interpretation of the studies was unanimous in all 10 cases. None of the subjects had diagnostic electrocardiographic changes or chest pain after dipyridamole.

Exercise electrocardiography (Table 2). Six (29%) of the 21 patients without significant coronary artery disease had a positive exercise stress test. Fifty patients with coronary artery disease had a positive exercise stress test. In 40 of these 50 patients, the dipyridamole echocardiography test was also positive.

Table 2. Correlation of Echocardiographic and Electrocardiographic Changes With Angiographic Findings

	Group				
	I (controls)	II	III	IV	V
CAD	0	0	1 Vessel	2 Vessel	3 Vessel
Symptoms	0	+	+	+	+
No. of patients	10	21	24	36	12
Echo +	0 (0%)	0 (0%)	12 (50%)	29 (81%)	12 (100%)
EST +	0 (0%)	6 (29%)	13 (54%)	26 (72%)	11 (92%)

CAD = coronary artery disease; Echo + = patients with positive dipyridamole echocardiography test; EST + = patients with positive exercise stress test; Symptoms = history of effort chest pain.

Twenty-two patients had coronary artery disease and a negative exercise stress test; 12 of them had a positive dipyridamole echocardiography test. None of these 22 patients had other signs suggestive of ischemia, such as complex ventricular ectopic activity or hypotension during the exercise stress test. Thirteen complained of mild to moderate chest pain. Eight did not attain at least 80% of their maximal age-predicted heart rate.

Correlations with angiographic findings (Table 2). All patients in whom transient wall motion abnormalities were observed had significant coronary artery disease. Each of these patients had a significant lesion in the coronary artery supplying the abnormal wall segment identified after dipyridamole. The dipyridamole echocardiography test (both low and high dose) is significantly more specific than the exercise stress test (100 versus 71%, $p < 0.05$); the exercise stress test is more sensitive (overall sensitivity 69%) than the low dose dipyridamole echocardiography test (53%), whereas the high dose test (sensitivity 74%, $p < 0.01$ compared with the low dose dipyridamole echocardiography test) closes the sensitivity gap.

Of the 22 patients with coronary artery disease and a negative exercise stress test, 12 had a positive dipyridamole echocardiography test; 4 of these patients had single, 7 had double and 1 had triple vessel disease (Fig. 3). Conversely, 10 patients, of the 19 with coronary artery disease and negative dipyridamole echocardiography test, had a positive exercise stress test: 6 of these patients had single and 4 had double vessel disease (Fig. 3).

Seventeen patients (five with a negative dipyridamole echocardiography test and four with a negative exercise stress test) had electrocardiographic evidence of prior myocardial infarction on the electrocardiogram at rest and regional asynergy on the baseline echocardiogram. Global sensitivity for the exercise stress test (ST shift and Q waves)

was 75%; global sensitivity for the dipyridamole echocardiography test (baseline and dipyridamole-induced asynergy) was 81%.

Discussion

The high dose dipyridamole echocardiography test is similar to the low dose test because it is feasible in all patients with a good baseline echocardiogram and it can detect ischemic segmental wall motion abnormalities in areas supplied by critically stenosed coronary arteries. The dipyridamole echocardiography and exercise stress tests can detect some patients with coronary artery disease overlooked by the other: 40 (56%) of 72 of our patients with coronary artery disease exhibited positive results in both tests, 10 (14%) of 72 tests were positive only in the exercise stress test and 12 (17%) of 72 were positive only in the dipyridamole echocardiography test. In particular, in these 12 patients with coronary artery disease and an inconclusive exercise stress test, the dipyridamole echocardiography test offered mechanical evidence of ischemia, thereby unmasking the elusive entity of electrocardiographically silent myocardial ischemia.

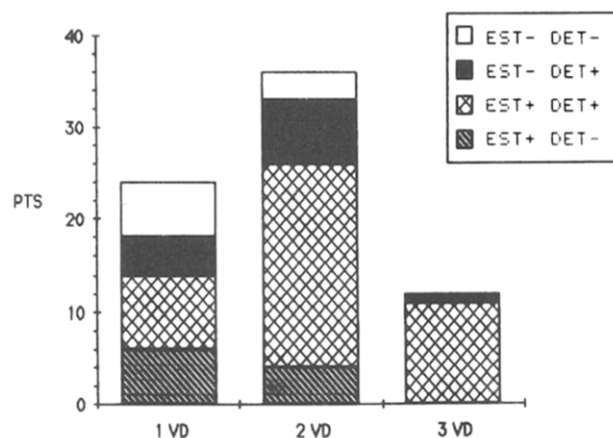
The high dose dipyridamole echocardiography test allows one to overcome the major limitation of the low dose test, that is, a relatively low sensitivity (53% in this study and 56% in a previous study on a different series of 66 patients) (1). The high dose dipyridamole echocardiography test adds sensitivity to the low dose test without any loss in specificity and with no apparent increase in risk.

Mechanism of regional asynergy induced by high dose dipyridamole. The most likely mechanism involved in the development of ischemia caused by dipyridamole is adverse redistribution of myocardial perfusion ("steal"), mostly from subendocardium to subepicardium (2). Because the individual response to the low dose dipyridamole is variable (4), the high dose could induce ischemia simply by achieving the maximal pharmacologic response, not attained with the low dose. In these patients, the higher dose might critically increase the achieved coronary dilation and the augmentation in flow might reduce the poststenotic perfusion pressure (12). This, in turn, causes a redistribution of coronary blood flow favoring subepicardial layers and may reduce absolute as well as relative subendocardial blood flow.

However, the higher dose of dipyridamole might also produce hemodynamic changes favoring the development of ischemia, especially in the presence of a maximally dilated coronary bed. In fact, the further decrease in aortic pressure and increase in heart rate, although relatively trivial, are possibly operating mechanisms orientated toward the creation of unfavorable perfusion conditions.

In almost all patients with a positive high dose test, a slight increase in rate-pressure product (at the onset of asynergy) with respect to the negative low dose test was observed. It is possible then that also the small increase in

Figure 3. Relative occurrence of positivity of the dipyridamole echocardiography test (DET) and exercise stress test (EST) in the 72 patients (PTS) with coronary artery disease, categorized according to the number of involved vessels. VD = vessel disease.



myocardial oxygen demand, as assessed by the increase in rate-pressure product, might play a role (although probably minor) in determining ischemia.

Feasibility of the test. In our study, we were able to obtain adequate echocardiograms after dipyridamole in all patients in whom an acceptable baseline study was possible. This is in sharp contrast with the considerable difficulty in obtaining adequate exercise echocardiograms (13-16). Several reasons may account for this fact: 1) the patient can lie comfortably and quietly in the position most suitable for echo monitoring, there is no need to remain supine or standing, as in exercise stress testing, and the patient stays relatively still; and 2) excessive tachycardia and particularly hyperventilation are absent, making it easier to obtain good quality recordings and to interpret them correctly.

Importantly, the test is not limited by physical disability, motivation or poor physical conditioning of the patient, any of which may severely limit or preclude the performance of dynamic exercise. It should be obvious, however, that dipyridamole infusion does not give information about exercise capacity and blood pressure response and that other complex physiologic changes present during exercise (such as the increase in coronary tone) (17,18) are not simulated.

Another limitation of the dipyridamole echocardiography test is that an adequate two-dimensional echocardiographic study in rest conditions cannot be obtained in all patients. In our study, 9 (9%) of 102 patients had poor quality echocardiographic images at rest and, therefore, were not enrolled in the study. In these selected cases, other noninvasive cardiac imaging techniques might be of some help to identify the diagnostic end point of a transient regional asynergy induced by dipyridamole infusion. Further studies are needed, however, to establish this point.

Safety of the dipyridamole dose employed. No significant arrhythmias, hypotension or other significant clinical complications occurred in any of the patients tested with the high dose of dipyridamole. The safety of the high dose test is more substantially documented by the wide clinical experience with similar doses, ranging from 0.75 to 1 mg/kg in 10 minutes (5-11). In a series reported by Osterspey et al. (9), up to 500 patients were studied with a dose of 0.75 mg/kg in 10 minutes, combined with electrocardiographic monitoring, and no significant complications were observed. Such experience is, however, less extensive than that gained with the lower dose, which is considered a diagnostic procedure even safer than exercise (19). It should also be noted that during the dipyridamole echocardiography test the patient lies in the recumbent position, and therefore there is no threat of orthostatic hypotension, the limiting factor with thallium-201 imaging combined with high doses of dipyridamole (2). Moreover, the high dose is applied only in selected patients in whom the low dose test has proved negative.

Last, the dipyridamole echocardiography test provides

a "mechanical" marker of the ischemic event. The detection of the asynergy is an end point of the test, and this allows us to stop the procedure without waiting for some usually "later" markers of ischemia, such as electrocardiographic changes, which can even be absent in some patients in the presence of obvious ischemia assessed by echocardiography. However, the safety of using higher doses of intravenous dipyridamole should be established more strongly in a larger patient series, particularly in patients with unstable angina or who are in the early postinfarction period.

Ischemia after dipyridamole infusion: how frequent an event? Our data appear to conflict with the currently accepted view that "dipyridamole produces little, if any, myocardial ischemia" (20). In fact, the thallium-201 dipyridamole test does not evoke (to be positive) myocardial ischemia as a diagnostic end point (2,21). Furthermore, pain and electrocardiographic changes are reported as relatively infrequent after dipyridamole infusion. For example, Albrow et al. (3) reported only a 3% occurrence of electrocardiographic changes; Leppo et al. (22) reported that only 10% of their patients with coronary disease had electrocardiographic changes. These findings seem to conflict with the 46 and 65% occurrence of ischemic electrocardiographic changes that we observed with the low and the high dipyridamole doses, respectively.

With this evidence of a high proportion of ischemic events, doubt could arise regarding a selection bias in the population we studied; it should be remembered, however, that all the patients in our study were not taking medication. In the study by Leppo et al. (22), the majority (85%) of the patients with coronary artery disease were taking a beta-blocker; this might substantially blunt the ischemic effects of dipyridamole while not significantly affecting flow changes, as indicated by clinical and experimental data (22,23). Furthermore, our data appear to be consistent with other studies reporting a high incidence of ischemia, both with the lower dose (62% prevalence of electrocardiographic ischemic changes in a series of 30 patients with coronary artery disease studied by Pirelli et al. [24]) and with the higher dose (0.75 mg/kg in 10 minutes) (80% positivity by electrocardiographic criteria or pain, or both, in a series of 396 patients with coronary artery disease reported by Osterspey et al. [9]).

Conclusion. The high dose dipyridamole echocardiography test offers valuable complementary information to the exercise stress test in patients with effort angina pectoris.

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